Seizure 23 (2014) 674–676

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Clinical letter

# An unusual case of drug-resistant epilepsy in a child with non-celiac gluten sensitivity

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ARTICLE INFO

*Article history:*
Received 23 February 2014
Received in revised form 4 April 2014
Accepted 7 April 2014

## 1. Introduction

Neurological manifestations of gluten sensitivity (epilepsy, cerebellar ataxia and peripheral neuropathy) are frequent and probably linked to an immunological attack to nervous tissues accompanied by neurodegenerative changes.[1]

A consensus document on new nomenclature and classification of gluten-related disorders identified celiac disease (CD), wheat allergy and non-celiac gluten sensitivity (NCGS), that neither meets the diagnostic criteria for CD nor those for wheat allergy.[1,2] Currently there are no specific biomarkers for NCGS, and the diagnosis is based on exclusion criteria.

NCGS incorporates a wide range of intestinal symptoms and of extra-intestinal symptoms, (headaches, lethargy and tiredness, attention deficit hyperactivity syndrome, autism, schizophrenia, muscular disturbances and bone and joint pain).[1]

The introduction of a gluten-free diet improves epilepsy in patients with confirmed or silent CD.[3,4] However, no studies have reported epilepsy in patients with NCGS. We describe a two-year-old boy who developed a neurological dysfunction with drug-resistant epilepsy in the setting of NCGS.

## 2. Case report

In September 2009, a two-year-old boy with unremarkable perinatal history, normal psychomotor development and a mild delay of language presented a first generalized tonic–clonic seizure. There was no family history of neurological diseases or epilepsy. Neurological examination and electroencephalogram (EEG) were normal. In August 2010, the boy presented a second seizure characterized by continuous blinking, eyes turned upward, and tonic–clonic movements of the upper and lower limbs; EEG during wakefulness or sleep and neurological examination continued to be normal. In a few weeks, epilepsy aggravated and daily polymorphic seizures (generalized tonic–clonic, myoclonic-astatic and absence seizures) appeared, suggesting a diagnosis of myoclonic astatic epilepsy.

The EEG began to show generalized spike-waves followed by high amplitude slow waves, mixed with spikes, over the anterior and central-parietal regions (Fig. 1A).

In October 2010, the child underwent brain MRI study that was normal. His general examination was unremarkable, but food allergies to dust mites, eggplant, tomato, potato, pepper and corn were found. Neurocognitive development was normal (developmental quotient = 96) but with a mild decline in language skills.

Antiepileptic drug therapy was started using clobazam, valproate, and ethosuximide. He continued to have seizures with worsening of behavior, irritability, and motor incoordination. Different antiepileptic drugs (AEDs) (lamotrigine, topiramate, levetiracetam) were added/substituted without any improvement. Complete neurometabolic and genetic tests and screening for the presence of the candidate gene SCN1A were negative.

Because of the resistance to all AEDs administered, we suggested a gastroenterologic evaluation, suspecting gluten hypersensitivity based on the presence of aphthae. Endomysial, anti-gliadin and anti-transglutaminase antibodies, IGE and IGA levels were within the normal range. Also the skin prick test for wheat allergy resulted negative. An esophagogastroduodenoscopy (EGD) with duodenal biopsy was planned but the parents denied

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http://dx.doi.org/10.1016/j.seizure.2014.04.005

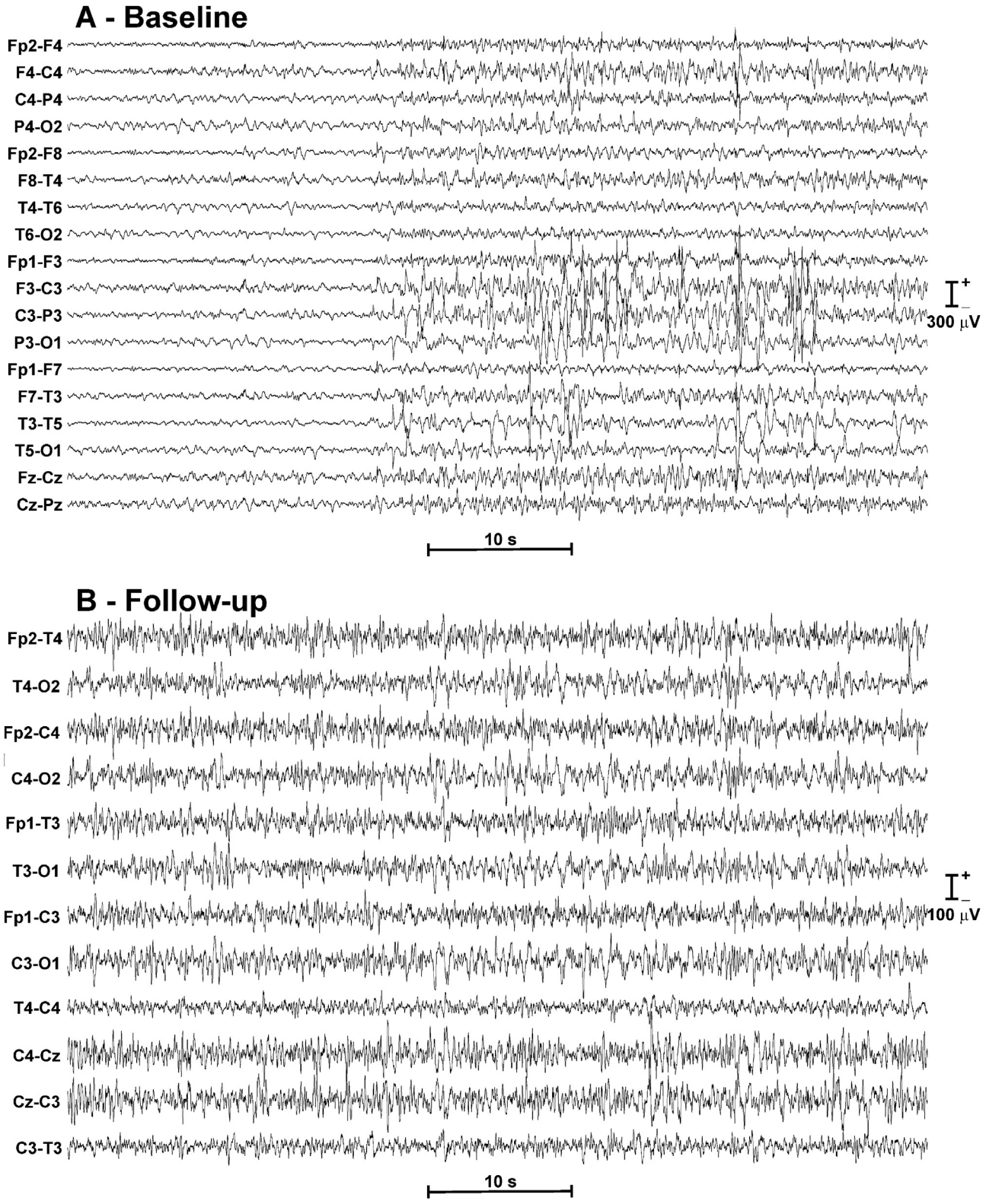


**Fig. 1.** (A) EEG during sleep showing generalized spike-waves followed by high-amplitude slow waves, mixed with spikes, over the frontal and central-parietal regions. (B) Normalization of the EEG during sleep six months after the introduction of a gluten-free diet.

authorization. HLA testing showed the presence of heterodimer DQ8 (DQA1*03, DQB1*03:02). Based on this finding we decided to adopt a gluten-free diet; informed consent was asked to the parents to begin the diet and, after, to withdraw AEDs. After two weeks, a gradual reversal of the clinical condition started: seizure frequency and intensity decreased, the child made progress in language and socialization with a decrease of hyperactive and aggressive behavior. Concurrently, in a few months the EEG showed a significant improvement with almost complete normalization. In November 2011, after 6 months from the beginning of the gluten-free diet, according to the clinical benefits, we started to reduce the dosage of AEDs till their complete withdrawal, in three

months. We finally suggested a gluten challenge test but again the parents denied the authorization. The boy did not have seizures, the EEG normalized and this condition persisted at follow-up, two years later (Fig. 1B).

## 3. Discussion

To our knowledge this is the first description of a child with drug-resistant epilepsy, language delay and aphthae in whom a gluten-free diet brought complete resolution of the seizures, normalization of the EEG, and a significant improvement in speech organization, even after the withdrawal of all antiepileptic drugs. Our patient showed no intestinal or extraintestinal symptoms, the only symptoms related to gastrointestinal discomfort were small whitish eruptions on the mouth and tongue, recognized as aphthae but not accompanied by fever, colic, or diarrhea. After the exclusion of the different causes of epilepsy, we tested the child for a CD but antibodies to gliadin, endomysium and transglutaminases were negative. HLA typing however showed the presence of the heterodimer DQ8 that allowed us to try a gluten-free diet, even without the diagnostic support of intestinal biopsy. The marked improvement of both epilepsy and language soon after the gluten-free diet that persisted even after the withdrawal of all antiepileptic drugs, lead us to hypothesize a NCGS neurological disease in our patient.

The clinical-EEG picture in this boy can be suggestive of mycolonic absence epilepsy or epileptic encephalopathy with atypical seizures and drop attacks. Dravet syndrome has been excluded for the clinical picture, seizure type (never presented with febrile seizures), EEG features and also the SCNA1 test was negative. Furthermore, several studies have shown a relationship between epilepsy and occult CD but these studies included patients that had epilepsy and after were discovered to be affected by CD.[3,4]

Our study has limitations: we could not perform intestinal biopsy (however, often the endoscopy and biopsy result normal in NCGS) nor gluten challenge because of the parents' refusal.

The consequence of this report could be the indication of a systematic screening for CD in all epileptic patients but obviously this is not practical or cost-effective; nevertheless, it seems reasonable to screen those with intractable seizures. According to this vision, we suggest to screen children with drug-resistant epilepsy for CD and, if negative, to evaluate HLA typing for the presence of heterodimer DQ2 or DQ8. These HLA genes are found in higher frequency in children with CD than in the general population. Although they are not diagnostic because 25–40% of the population has positive results, positive DQ2 or DQ8 in young children might be a marker of neurologic involvement of gluten sensitivity and could reflect an increased likelihood for the development of refractory seizures at early ages and, presumably, CD at later ages.

## Conflict of interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## Authors' contributions

All coauthors have been substantially involved in the study and/or the preparation of the manuscript; and no undisclosed groups or persons have had a primary role in the study and/or in manuscript preparation and all coauthors have seen and approved the submitted version of the paper and accept responsibility for its content.

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